REMARKS

Claim 4 is further amended herewith to clarify the claimed invention and to sharpen its definition over the prior art of record.

In particular, claim 4 now recites that:

(1) the target prokaryotic or eukaryotic cell does not comprise the nucleic acid of interest at the target nucleotide sequence prior to transfection;

(2) a DNA vector that is replication competent in the target prokaryotic or eukaryotic cell and comprises the nucleic acid of interest is contacted with a mutagenic agent blocking intracellular DNA replication of said DNA vector, to produce a modified DNA vector; and

(3) transfection of the target prokaryotic or eukaryotic cells is effected with the modified DNA vector and under conditions wherein replication of the modified DNA vector commences and insertion of the nucleic acid of interest within the predetermined target nucleotide sequence occurs.

Support for the production of a modified DNA vector by contact with the mutagenic agent may be found for example at p. 7, lines 22-26; p. 9, lines 22-24; and p. 19, lines 30-35 of the specification. Support for the transfection of the target cells being performed under conditions wherein replication of the modified DNA vector commences and insertion of the nucleic acid

of interest within said predetermined target nucleotide sequence occurs may be found for example at p. 4, lines 8-19 and p. 23, lines 3-5 of the specification.

Turning now to the repeated prior art rejections, applicants note that the Official Action does not dispute the factual accuracy of the previously-stated distinctions between the method of the present claims and the applied references, but rather considered that those arguments were not adequately reflected in the previous language of the claims. The present amendments to claim 4 now more clearly reflect those distinctions.

Claims 4-6, 10-14, 16-18, 21 and 22 were rejected under 35 USC §102(b) as allegedly being anticipated by Hinds et al, "Enhanced gene replacement in mycobacteria", Microbiology, 1999, Vol. 145, pp. 519-527. That rejection is respectfully traversed, for the following reasons.

The plasmid vectors that are treated with UV radiation in Hinds are suicide vectors, which therefore are not replication competent and do not replicate in the *M. smegmatis* cells into which they are introduced.

Thus, Hinds fails to disclose at least the following recitations in present claim 4:

1. Contacting a DNA vector that is replication competent in the target prokaryotic or eukaryotic cell with a mutagenic agent, to produce a modified DNA vector; and

2. Transfecting the target prokaryotic or eukaryotic cells with the modified DNA vector under conditions wherein replication of said modified DNA vector commences.

The Official Action calls attention to the third paragraph on page 524 of Hinds, which describes that, in addition to using denatured DNA in a pY6002 vector, the effect of using ss phagemid DNA in a pSYCH09 vector was assessed. However, Table 1 on p. 520 of Hinds confirms that pSYCH09, like pY6002, is a suicide vector, such that neither vector is replication competent in the *M. smegmatis* cells of Hinds, nor does replication of either vector commence in those cells. Moreover, the reference does not disclose that the ss phagemid DNA replicates in the *M. smegmatis* cells of Hinds.

The Official Action notes at p. 6 that the open claim language "comprising" indicates that the method may have additional steps, which is correct; however, the relevant inquiry in assessing the applicability of an anticipation rejection is whether the prior art discloses the steps that are recited in the method as claimed, regardless of whether the method as performed could include steps described in the prior art.

For the reasons discussed above it is believed to be clear that Hinds does not describe the steps recited in claim 4, and that the rejection of Claims 4-6, 10-14, 16-18, 21 and 22 as being anticipated by Hinds should therefore be withdrawn.

As to the rejection of claims 4-5, 10-14, 16-19, 21 and 23 under 35 USC §102(b) as anticipated by GANIATSAS, as noted previously the heat shock or UV exposure described in that publication is performed after the alteration of the genome of the ES cell line and the selection and propagation of the altered cell line to a sufficient density so as to allow western blot analysis to be performed.

By contrast, it is believed to be even more clear in claim 4 as amended herewith that the treatment of the DNA vector with the mutagenic agent occurs before the cell containing the target sequence is transfected. Claim 4 as amended herewith also now makes explicit that the nucleic acid of interest is integrated into the chromosomal DNA and that replication of the DNA vector commences in the target cell ("under conditions wherein replication of said modified DNA vector commences and insertion of the nucleic acid of interest within said predetermined target nucleotide sequence occurs").

Regarding the comment in the Official Action concerning the open transitional language of the present claims, applicants note that the failure of Ganiatsas to disclose a method in which

a target cell is transfected with a DNA vector that has been modified prior to transfection by contact with a mutagenic agent renders the reference non-anticipatory regardless of what steps could be performed in addition tot hose recited.

As GANIATSAS does not disclose at least these aspects of claim 4, it follows that none of claims 4-5, 10-14, 16-19, 21 and 23 is anticipated by that reference.

Lastly, as to the rejection of claims 4-21 and 23-24 under 35 USC §102(e) as anticipated by HOEIJMAKERS, the exposure of the altered and unaltered cells of that reference to a DNA lesion inducing agent such as UV, applicants note again that occurs only once suitably and stably transformed cells have been created, selected and propagated into whole animals from which further samples can be derived.

Again, claim 4 as amended herewith is believed better to reflect these differences between the present invention and the disclosure of HOEIJMAKERS in its recitation that the DNA vector containing the nucleotide sequence of interest is treated with a mutagenic agent to produce a modified DNA vector, and it is this modified DNA vector that is used to transfect a target prokaryotic or eukaryotic cell. As HOEIJMAKERS does not disclose at least this aspect of claim 4, it follows that none of claims 4-21 and 23-24 is anticipated by that reference.

In view of the present amendment and the foregoing remarks, it is believed that this application is now in condition for allowance with claims 4-24, as amended. Allowance and passage to issue on that basis are accordingly respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,
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